Best Practice & Research Clinical Gastroenterology
Vol. 19, No. 1, pp. 3–23, 2005
doi:10.1016/j.bpg.2004.10.004
available online at http://www.sciencedirect.com

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Epidemiology and natural history of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is a major contributor to cancer incidence and mortality. There is a wide variation, however, in the global distribution of HCC. Eighty percent of the burden is borne by countries in Asia and sub-Saharan Africa. In most high-risk countries, principal risk factors include infection with hepatitis B virus and dietary exposure to aflatoxin B_1. In contrast, hepatitis C virus and alcohol consumption are more important risk factors in low-risk countries. In recent years, the incidence of HCC has decreased in some high-risk countries and increased in some low-risk countries. Reasons for both trends are not completely understood, but are likely related to public health efforts in Asia and the increase in hepatitis C virus infection in low-risk countries. Vaccination programs against hepatitis B virus will likely decrease the HCC rate even further in decades to come.

Key words: hepatocellular carcinoma; incidence; hepatitis B virus; hepatitis C virus; aflatoxin B_1.

Primary liver cancer is the fifth most common cancer in the world and the third most common cause of cancer mortality.[1] Approximately 560 000 cases are diagnosed each year and 550 000 deaths due to liver cancer occur. In most countries, 75–90% of liver cancers are hepatocellular carcinomas (HCC)[2], thus trends in liver cancer incidence and mortality tend to reflect trends in HCC incidence and mortality.

INCIDENCE AND MORTALITY

There is wide geographic variability in HCC incidence (Figure 1). The great majority of liver cancer (>80%) occurs in either sub-Saharan Africa or in Eastern Asia, with one

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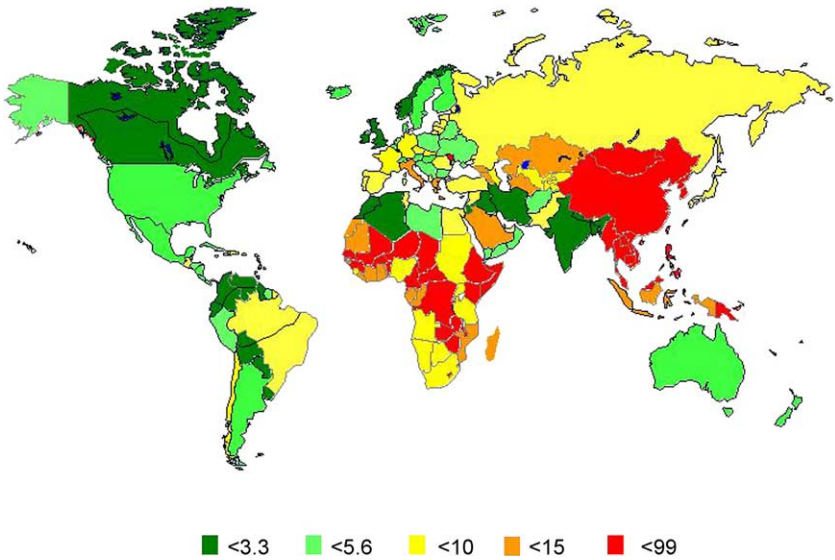

Figure 1. Global incidence of liver cancer in males, 2000 (Parkin, 2001).

country alone, China, accounting for over 50% of cases. With some exceptions, countries in North America, South America, Northern Europe and Australia tend to have low incidence rates while countries in central and southern Europe tend have intermediate rates.[3] The cancer registry reporting the highest liver cancer rates in the world is in Qidong, China, where male incidence is 95.7/100 000 and female incidence is 29.6/100 000. Very high rates are also reported from the Khon Kaen registry of northeast Thailand (male: 88.0/100 000; female: 35.4/100 000), but most liver cancers in that region are intrahepatic cholangiocarcinomas rather than HCCs.

Over the past several decades, declining trends in HCC incidence have been seen in some high-rate areas.[4] Between 1978–1982 and 1988–1992, decreases in incidence were seen among Chinese populations in Hong Kong, Shanghai and Singapore. Decreases continued in the subsequent 5-year time interval, 1993–1997, in all three locations.[5] In addition to these areas, Japan also began to experience declines in male rates during the 1993–1997 interval. Female rates in Japan continued to increase in the 1993–1997 interval but the rate of increase declined. Less information is available on HCC trends in Africa as few registries in that region have long-term data.

In contrast to trends in some high-risk areas, registries in a number of low-rate areas reported increases in incidence between 1978–1982 and 1993–1997.[4] Included among these registries are those in Australia, the US, Canada and the UK. Reasons for both the decreased incidence in high-rate areas and increased incidence in low-rate areas are not certain. It has been widely suggested, however, that the increased incidence in low-rate areas, may be related to increased prevalences of HCV infection.

Survival rates of primary liver cancer are uniformly poor in both high-rate and low-rate areas. The International Agency for Research on Cancer (IARC) estimates that the age-standardised worldwide incidence rate of primary liver cancer among males is 17.4/100 000 in underdeveloped countries and 8.7/100 000 in developed countries.

The comparable mortality rates are 16.8/100 000 and 8.1/100 000, indicating very little difference in survival in the contrasting areas.[3]

DEMOGRAPHIC FACTORS

Age

The global age distribution of HCC varies by incidence, gender and, possibly, also by etiology.[5] In almost all areas, female incidence rates peak 5 years older than the peak age of male rates. In low-risk populations, the highest age-specific rates occur among persons aged 80 years and greater. A similar correlation of risk and age is seen among most high-risk Asian populations (e.g. Hong Kong, Shanghai, Singapore). In contrast, male rates in high-risk African populations (e.g. The Gambia, Bamako, Mali) tend to peak between ages 60 and 65 years before declining; while female rates peak between 65 and 70 years before declining.

Exceptions to these age patterns occur among the high-rate populations of Japan and Qidong, China. In Japan, male incidence rates peak at age 65 and then, plateau, while female rates plateau after age 70 years. In Qidong, China, the age-specific male incidence rates rise until age 45 and then plateau. Among females in Qidong, the incidence rates rise until age 60, before plateauing.

The different age patterns of HCC incidence in different areas are most likely related to the dominant hepatitis virus in the population, the age at viral infection, existence of other risk factors, and cohort effects. In Japan, the dominant virus is hepatitis C virus (HCV), while in Qidong, China, the dominant virus is hepatitis B virus (HBV). Most persons infected with HCV were infected as adults. Most HBV carriers in Qidong and elsewhere became infected at a very young age. The explanation for the younger age peaks in Qidong and Japan, in contrast with other populations having similar viral exposures is not clear, but may be due to the existence of other hepatocarcinogenic exposures.

Sex

In most areas of the world, the incidence of HCC among men is two to four times higher than the incidence among women. The greatest differences between male and female rates no longer occur among high-risk HCC populations[1], but among the populations of central and southern Europe.[4] Typical among these male:female ratios are the ones reported from Calvados, France (8.8:1), Geneva, Switzerland (7:1) and Trieste, Italy (4.8:1). In contrast, typical ratios currently seen in high-risk populations are those of Qidong, China (3.7:1), Osaka, Japan, (4.0:1), Kangwha, Korea (3.6:1), and Hanoi, Vietnam (4.1:1). The only registries in the world that report ratios at or near 1:1 are in South America (Cali, Colombia; Quito, Ecuador; and Lima, Peru). The more pronounced male:female ratios currently found in low- to medium-rate areas may be related to the changing rates in these regions as male rates are increasing somewhat faster than female rates in low-risk areas and decreasing somewhat faster than female rates in high-risk areas.

The reasons that males have higher rates of liver cancer than females are not completely understood, but may be partly explained by the sex-specific prevalence of risk factors. Males are more likely to be infected with HBV and HCV, consume alcohol,

smoke cigarettes, and have increased iron stores. Androgenic hormones and increased genetic susceptibility may also increase risk among males.

Ethnicity

HCC incidence rates can vary greatly among persons of different ethnicities living in the same region. For example, Korean men living in Los Angeles have incidence rates more than 5 times higher than white men.[4] Similarly, in Singapore, Chinese men have rates 2.7 times greater than Indian men, while in San Francisco, Chinese men have rates 4.2 times the rate of white men. The ethnic differences in rates among men are equally true of rates among women. This variation almost certainly reflects differences in the likelihood of infection with HBV and HCV, although genetic susceptibility and different patterns of exposure to other risk factors may also play a role.

ENVIRONMENTAL RISK FACTORS

The major, well-established risk factors for HCC are chronic infection with HBV or HCV, dietary exposure to aflatoxin B_1 AFB_1-contaminated foodstuffs and consumption of alcohol. In high-rate HCC areas, HBV and AFB_1 are the dominant factors, whereas HCV and alcohol are more important factors in low- to medium-rate areas (Table 1). Overall, it is estimated that HBV and HCV infections are causally associated with over 80% of HCC in the world.[6]

Hepatitis B virus

Approximately 5% of the world's populations (350 million people) are chronically infected with HBV; the majority of whom reside in the HCC high-risk regions of Asia and Africa. In most such regions, with the exception of Japan, HBV infection is associated with most cases of cirrhosis and 80% or more of the cases of HCC. The lifetime risk of HCC in infected men is estimated to be between 10 and 25%, while the risk in infected women is somewhat lower. Evidence supporting the causal association of HBV and HCC has been assembled over more than 20 years and led IARC to classify HBV as carcinogen in humans in 1994.[7] A brief summary of the evidence is presented below.

Animal viruses belonging to the same family as HBV (hepadnaviruses) cause HCC in their natural hosts. In a defining experiment, inoculation of newborn woodchucks with

Table 1. Relationship between selected factors and risk of hepatocellular carcinoma.

Evidence	Decreases risk	Increases risk
Convincing		Hepatitis B virus, hepatitis C virus, aflatoxin B_1, cirrhosis, alcohol, male gender, hemochromatosis, thorotrast
Probable	Vegetables	Iron levels, vinyl chloride, obesity, diabetes mellitus
Possible	Selenium, green tea	Tobacco, anabolic steroids, androgen levels, parity, schistosomiasis, NASH
Unclear		Arsenic

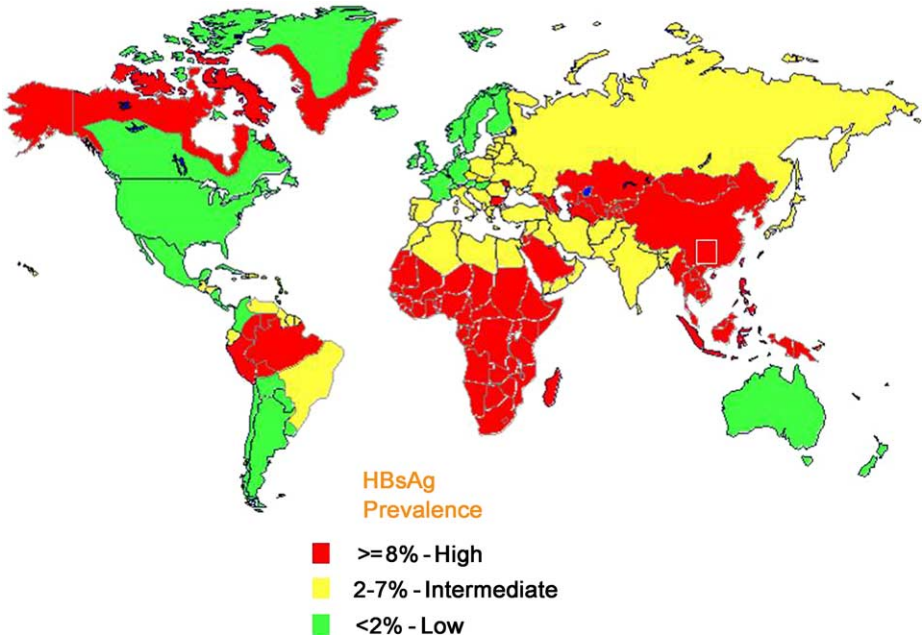

Figure 2. Geographic distribution of chronic HBV infection, 2000 (CDC, 2002).

woodchuck hepatitis virus resulted in chronic infection with the virus and HCC within 3 years.[8]

Areas of the world with high HCC rates have high prevalences of chronic HBV infection and the reverse is also true (Figures 1 and 2).[1,9] In high-rate HCC regions, cirrhosis is closely associated with chronic HBV infection and cirrhosis precedes almost all cases of HCC.[10] Case-control studies in all regions of the world have consistently shown that chronic HBV infection is much more common among HCC cases than controls, with odds ratios ranging from 5:1 to 65:1.[7] Similarly, prospective studies of persons chronically infected with HBV have demonstrated very high relative risks for HCC, ranging from 5 to 103.[11] Among chronically infected persons who develop HCC, HBV is universally present in the liver tissues.

In high-rate HCC and HBV areas, roughly 70% of HBV infections are acquired either in the perinatal period or in early childhood.[12] Studies have shown that HBV carriers born to HBV infected mothers are at higher risk of HCC than other HBV carriers.[13] The increased risk is likely to be related to a longer period of infection. Finally, prevention of infection with HBV reduces the risk of subsequent HCC. Following universal vaccination of neonates in Taiwan, the incidence of HCC among children declined from 0.7 to 0.36 per 100 000.[14]

Hepatitis C virus

Hepatitis C virus (HCV) was identified in 1989 and reliable tests for HCV antibodies and HCV RNA became available soon after. Similar to HBV, HCV may cause a chronic infection of very long duration, accompanied by slowly evolving liver disease.

Unlike HBV, HCV infection is usually acquired in adulthood and acute HCV infections are usually silent.

In 1994, IARC classified HCV as a human carcinogen.[7] The strongest evidence for a causal link between HCV and HCC comes from Japan. Before the identification of HCV, Okuda et al[15] hypothesised that a non-A, non-B (NANB) virus caused a significant proportion of HCC in Japan. The hypothesis was based on the fact that although the incidence of HCC had more than doubled between 1966 and 1983, the proportion of HCC linked to HBV had declined from 50 to 30%. When assays for HCV antibodies became available, the hypothesis was proven correct.[16] Subsequently, prospective data on the risk of HCC in Japan were reported in a study of 2890 HCV patients.[17] The annual incidence of HCC among patients with concomitant cirrhosis was 7.9% while the incidence was only 0.5% among patients with little or no fibrosis.

In other areas of the world, studies of patients with chronic hepatitis and/or cirrhosis confirmed that HCC can be an outcome of long-term HCV infection. The proportion of patients who develop HCC, however, varies by country of report, length of follow-up, and prevalence of cirrhosis. In almost all cases, cirrhosis precedes the diagnosis of HCC.

Four studies have been published of individuals whose time of exposure to HCV is known. Seef et al[18] ascertained long-term mortality among five separate studies of transfusion-associated hepatitis conducted from 1967 to1980 in the US. An average of 18 years after transfusion, neither all cause mortality (51%) nor HCC mortality (0.2%) differed in patients who had developed NANB hepatitis and patients who had not. After 25 years of follow-up in a subset of the cohorts, all-cause mortality remained equal between the groups. Three deaths from HCC had occurred in the HCV(+) group while no HCC deaths had occurred in the HCV(−) group. In a second study by Seef et al[19], 8568 serum samples, stored since 1948–1954, were tested for HCV. Only 17 samples were anti-HCV positive, while 11 were HCV RNA positive. After 50 years, mortality was higher among the 17 HCV-infected persons (41%) than among the HCV negative population (26%), though no HCC deaths had occurred.

Two other studies in which the time and source of exposure to HCV are known have been reported. Both resulted from administration of HCV-contaminated Rh immune globulin. In Ireland, among 704 HCV-infected women followed for 17 years, no cases of HCC developed.[20] Similarly, 1018 HCV infected women in Germany were followed for 20 years and no cases of HCC occurred.[21] These studies from the US, Germany and Ireland indicate that the very high rate of HCC among HCV infected persons in Japan may not be typical and may be related to exposure to alcohol and/or other risk factors.

Synthesising the data from both clinical and population-based studies, Alter and Seef[22] proposed a natural history model of HCV. Among persons acutely infected, 20% would spontaneously recover and 80% would develop a persistent infection. Among those with a persistent infection, 30% would develop severe progressive hepatitis and 70% would develop either stable chronic hepatitis or a very slowly progressive liver disease. These projections are similar to those of the WHO[23], which proposed that 20% of the individuals initially infected with HCV would develop cirrhosis and 2–4% HCC.

Several factors affect the rate of progression of chronic liver disease among HCV-infected individuals. Like HBV, males appear to be at higher risk of HCC.[24] Males are more likely to engage in high-risk behaviors for acquiring co-infections with HBV and HIV, which may also increase risk of HCC. In contrast to HBV, older age (greater than 40 years) at infection is associated with an increased risk of HCC.[25] Alcohol intake has been consistently found to increase risk of HCC among HCV(+) individuals.[26]

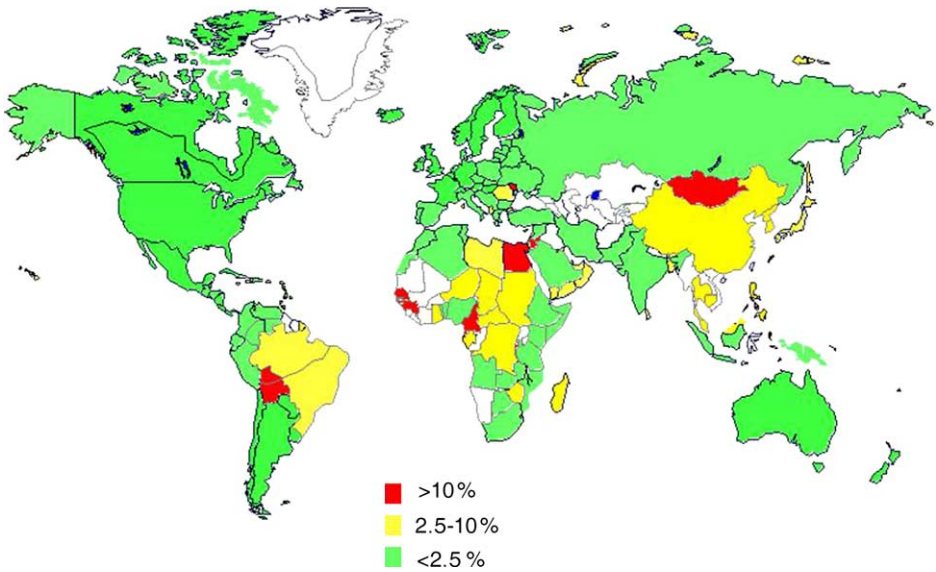

Figure 3. Global distribution of chronic HCV infection, 2001 (WHO, 2001).

Globally, about 170 million people (3% of the world's population) are chronically infected with HCV and 3–4 million are newly infected each year.[27] Seven to 9 million of the 170 million currently HCV infected people will likely die of HCC. Because HCV infection is less common than HBV infection, however, the world distribution of chronic HCV infection (Figure 3) is quite different from that of HCC mortality (Figure 1).

Aflatoxin

Aflatoxin B_1 (AFB_1) is a mycotoxin elaborated by fungi of the *Aspergillus* species. The fungi grow readily on foodstuffs, such as corn and peanuts, stored in warm, damp conditions. Although there are four principal aflatoxins, B_1, B_2, G_1, and G_2, AFB_1 is the most potent in animal studies.[28] In 1987 IARC classified aflatoxin as a human carcinogen.[28]

Once ingested, AFB_1 is metabolised to an active intermediate, AFB_1-*exo*-8,9-epoxide, which is later detoxified through a variety of metabolic processes. The intermediate epoxide has been shown to bind and damage DNA, primarily at the N7 position of guanine.[29] The characteristic genetic change associated with AFB_1 is a G to T transversion in the third base of codon 249 of the p53 gene.[30] The p53 249^{ser} mutation has been observed in 30–60% of tumours arising in persons living in high aflatoxin areas.[31,32]

Many ecological studies of AFB_1-contamination of food conducted in the 1970s and 1980s were compatible with a role for the carcinogen in HCC. Stronger evidence of an AFB_1–HCC link was supplied subsequently by studies based on the detection of AFB_1 markers in biosamples. Further, an interaction of AFB_1 and HBV infection on HCC risk was revealed in short-term prospective studies in Shanghai, China.[33] From that study, it was estimated that AFB_1 increased the risk of HCC four-fold, HBV increased the risk

seven-fold, and the combination of AFB_1 and HBV increased the risk 60-fold. More recent studies in the high-AFB_1 contamination area of Qidong, China have reported similar results.[34]

In most areas of the world where AFB_1 exposure is widespread, chronic HBV infection is also highly prevalent. Though HBV vaccination is these areas should be the major preventive tactic, persons already chronically infected with HBV will not benefit from vaccination. HBV carriers could benefit, however, by eliminating AFB_1 exposure. Efforts to accomplish this goal in China[35] and Africa[36] have been launched.

Alcohol

The evidence in support of a positive association between alcohol consumption and HCC led IARC to conclude in 1988 that there was a causal relationship.[37] The mechanism by which alcohol increases risk is not well understood, however. Other unresolved issues include the comparative risk in men versus women and the combined effect of alcohol and HBV vs. the effect of alcohol and HCV

Earlier studies of HCC found alcohol to be a more significant risk factor in low incidence areas than in high incidence areas. This may have been due to lower mean alcohol consumption in high-risk populations and/or due to the dominant effect of chronic HBV infection masking any additional risk of alcohol consumption. While some studies in HBV-endemic populations have shown a positive association between alcohol consumption and HCC[38], other studies have not.[39] In comparison, most studies in populations where HCV is the dominant virus have found alcohol to be a significant risk factor.[40] Recent studies have reported little difference in the risk imposed by alcohol and HCV in comparison with alcohol and HBV.[41] Data also suggest that alcohol is associated with HCC in the absence of either HBV or HCV infection, though higher levels of consumption are probably required for HCC in the absence of viral infection.[41]

Whether alcohol is more strongly associated with HCC in women than in men has been difficult to study given that women are less likely to be heavy drinkers and less likely to develop HCC than men. A greater effect of alcohol on women has been hypothesised based on differences in alcohol dehydrogenase activity[42] and evidence of a greater association between alcohol and cirrhosis among women.[43] No substantial sex difference in risk of HCC with alcohol consumption, however, was reported in the Brescia study.[41]

The mechanism by which alcohol increases HCC risk is not well understood. Animal and human studies provide little evidence that ethanol is a carcinogen.[44] Some of the mechanisms by which alcohol might increase risk include the production of acetaldehyde and free radicals during alcohol metabolism, cytochrome p4502E1 induction, modulation of cell regeneration, promotion or exacerbation of nutritional deficiencies and alterations of the immune system.[45] It is certain that alcohol induces cirrhosis and cirrhosis is a factor in 60–90% of HCCs. Whether alcohol is related to HCC independent of cirrhosis is less clear.

Tobacco

The effect of cigarette smoking on risk of HCC has been extensively studied, yet the results remain inconclusive. Of more than 50 studies that examined the association between 1983 and 2004, approximately equal numbers reported a positive association as reported no association. A number of studies have reported that the tobacco effect

was limited to a subset of the study population defined by HBV status, HCV status, genetic polymorphisms or other exposures. The accumulated evidence is compatible with a weak association between smoking and HCC that is probably limited to subset of the general population.

Iron

The evidence that higher body iron stores may increase the risk of HCC comes from several sources. Persons with inherited metabolic disorders characterised by hepatic iron loading (e.g. hemochromatosis, porphyria cutanea tarda) are at increased risk of HCC.[26,46] Similarly, iron overload in Africans, unrelated to hemochromatosis, has been associated with an increased risk of HCC.[47] In addition, studies of persons at high-risk of HCC due to exposure to HBV, HCV and alcohol have suggested that iron may be a co-factor.

Endogenous and exogenous hormones

A relationship between oral contraceptive (OC) use and benign hepatic adenoma is well established. The evidence suggests that there is also a relationship between OC use and HCC. Although cohort studies have not reported significant risks[48], case-control studies have found increased risks with long-term OC use (>5 years).[49] Most studies have found that risk is limited to OC use in the absence of viral infections.[49] Contrary to the evidence for OC use, neither injectable progestogen use nor post-menopausal hormone replacement use have been associated with risk of HCC.[50]

Evidence from case reports suggests that anabolic steroids may cause HCC[51], but no epidemiologic study of anabolic steroids and HCC has yet been reported. Due to the scarcity of data, IARC has classified the evidence for carcinogenicity in humans as 'limited'.[28]

A role for endogenous hormones in the etiology of HCC has been proposed to explain the male excess of HCC in almost all countries. Experimental animal studies have supported a role for androgens in hepatocarcinogenesis[52], but whether androgens are also a risk factor in humans is not clear. In studies conducted in Taiwan, Yu and Chen[53] reported a positive association between increased testosterone levels and HCC among men chronically infected with HBV. In a study that examined both HBV-infected and uninfected men, Yuan et al[54] found that infected men had significantly higher testosterone levels than uninfected men and suggested that the difference might explain the testosterone–HCC relationship.

Among women, several studies found that HCC risk increased with increasing parity.[55,56] The mechanism by which increased parity would increase HCC risk is not clear, but may be related to the altered estrogen profile in pregnancy[57], or to the promotional effect of estrogens on a liver that is chronically infected with HBV. In support of a role for estrogen are recent data showing an increased risk of HCC among women with younger ages at menarche and older ages at menopause.[58]

Diet

Although few dietary items have been extensively examined in human studies, decreased risks of HCC have been reported in association with selenium, tea and vegetable consumption. Selenium (Se) has been most widely studied in Qidong, China

due to a geographic correlation between high HCC rates and low serum Se levels. Three Se-supplementation trials reported a decrease in both HCC and in the HBV carrier rate in Qidong.[59] In addition, a cohort study in Taiwan reported that men who developed HCC had lower selenium levels at study enrollment than did men who did not develop HCC.[60] In contrast, a geographic correlation study in China reported no correlation between plasma selenium levels and liver cancer mortality.[61]

Several studies in animals have shown that green tea consumption decreased the risk of liver cancer.[62] Few human studies have been reported (Evans et al[11]), but the combined results suggest that green tea may be protective, particularly among persons who are also exposed to alcohol and tobacco.[63]

An inverse association between vegetable consumption and risk of HCC has been supported by at least seven studies[64] conducted in Japan, Taiwan, Hong Kong, Thailand and Italy. Conversely, several studies reported no association.[64] The combined evidence led the World Cancer Research Fund and the American Institute of Cancer Research to conclude that diets high in vegetables probably reduce the risk of HCC.[64]

Schistosomiasis

Schistosomiasis, caused by infestation with trematode blood flukes, is endemic in tropical areas of Africa, South America, Asia and the Caribbean. Three species of schistosomes, *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma mekongi* preferentially infect the liver, however, only *S. japonicum* has been classified by IARC as possibly carcinogenic in humans.[7] More recently reported studies have supported a role for *S. japonicum* infection in HCC as a cofactor with HBV and HCV infections rather than as a primary hepatocarcinogen.[65]

Thorotrast

Persons exposed to Thorotrast, an X-ray contrast medium once used for cerebral angiography and liver-spleen scans, receive chronic, low-level, internal exposure throughout the liver, primarily to alpha-particle radiation. Follow-up of Thorotrast-exposed cohorts[66] has found a 120-fold increased risk of primary liver cancer, largely due to risks of angiosarcoma and intrahepatic cholangiocarcinoma. While the risk of developing HCC is not as great, evidence from Japan suggests that the proportion of Thorotrast-associated liver tumours that are HCCs has increased over time.[66]

Vinyl chloride

Occupational exposure to vinyl chloride (VC) is a recognised risk factor for angiosarcoma of the liver. Follow-up of occupational cohorts indicates that extremely high levels of exposure are necessary for tumour induction. Some studies have also reported weaker associations between VC and HCC that may require the presence of other risk factors.[67]

Arsenic

The association between inorganic arsenic and angiosarcoma of the liver is well established. Whether arsenic is also a risk factor for HCC is less clear. A series

of studies done in a high arsenic area of Taiwan have reported increased liver cancer rates[68], but those findings have not been replicated in other areas of the world.[69]

HOST FACTORS

Cirrhosis

The great majority of HCCs are associated with cirrhosis. Chronic liver disease of all etiologies is characterised by varying degrees of inflammation and fibrosis. The degree or stage of fibrosis appears to correlate best with prognosis. Although various classifications of fibrosis have been proposed, there is general agreement that cirrhosis is the most advanced stage of fibrosis. It is characterised histopathologically by nodules (pseudolobules) of hepatocytes surrounded by dense bands of fibrous tissue.[70] In addition, cirrhosis is classified by five variables; serum bilirubin, serum albumin, ascites, neurological impairment (encephalopathy), and prothrombin time, into three degrees of clinical compensation (Child-Turcotte-Pugh score) A, B, and C.[71] Patients with Child A cirrhosis have normal or near normal values for the five criteria and are considered well compensated, Child B have moderately abnormal values and C are severely impaired. Published prospective studies have rarely included patients with Child C disease.

Because cirrhosis is diagnosed definitively by liver biopsy, few population-based or unbiased prospective studies have been done to demonstrate the rate at which HCC develops in cirrhotic livers. One exception is the Dionysos study in which 6917 persons in northern Italy were enrolled in a population-based liver disease study.[72] Of 78 persons identified with cirrhosis at study enrollment, eight developed HCC in the ensuing 9 years.[73] Among the 81 persons infected with HBV, none developed HCC, while five HCV(+) persons who had cirrhosis developed HCC. Among 1349 people without HBV or HCV who consumed more than 30 g of alcohol per day; two developed HCC.

The largest study of cancer among persons with cirrhosis was conducted in Denmark by linking the Danish National Registry of Patients with the Danish Cancer Registry.[74] Among 110 individuals with cirrhosis, 199 HCCs in 11,605 individuals were diagnosed compared with 3.3 expected, resulting in a standardised incidence rate of 60. Similarly, Velazquez et al[75] prospectively followed 463 patients with Child A or B cirrhosis for the development of HCC. During a mean follow-up of 3.2 years, 38 patients were diagnosed with HCC, yielding a mean annual incidence of 2.95%. Other investigators also concluded that the yearly risk of HCC among patients with cirrhosis is about 3%.

Immune function

Since the early 1980s, many persons have become co-infected with human immunodeficiency virus (HIV) and HBV or HCV, causing severe immunodeficiency. With the introduction of HAART (highly active anti-retroviral therapy) in the mid 1990s, the degree of immunodeficiency was reduced and survival time lengthened. Several studies have now examined the hypothesis that immunodeficiency increases the risk of liver cancer.[76–78] Frisch et al[76] analysed the rate of liver cancer in 302 834

individuals with AIDS in the US and, based on a number of HIV epidemic-modeling assumptions, concluded that the risk was not increased. In the UK, a cohort study of males with haemophilia (many co-infected with HIV and HCV) who were treated with blood products before 1985 and followed to 1993, revealed a 5.6-fold increased mortality for liver cancer.[78] Other cohort studies reported increased deaths from liver disease among HIV/HBV and HIV/HCV co-infected haemophilia patients or injecting drug users, but did not specifically identify HCC or liver cancer among the causes of death. HIV is known to accelerate progression of liver fibrosis to cirrhosis in both HBV- and HCV-infected individuals.[79] Since cirrhosis is the precursor to HCC in most cases and since survival time has increased greatly in the HAART era, it is quite possible that co-infection with HIV will have a major impact on HCC risk in the future.

Genetic susceptibility

Genetic susceptibility studies have most often focused on genes that encode enzymes in the aflatoxin B_1 (AFB_1) detoxification pathways, principally the glutathione-*S*-transferases (GST) and epoxide hydrolases (EPHX). Inconsistent findings have been reported for the most commonly examined GST loci, GSTM1, GSTT1 and GSTP1. GSTA4, was associated with HCC risk, but has been examined in only one study to date.[80] Most studies of epoxide hydrolase 1 (EPHX1) do not support an association with HCC, but there may be an association with EPHX2.[80] Conflicting findings have also been reported for polymorphisms in *N*-acetyltransferase 1 and 2 (NAT1, NAT2).[81,82]

Because alcohol is a recognised risk factor for HCC, polymorphisms in the alcohol metabolising enzymes, alcohol dehydrogenase 2 (ADH2) and aldehyde deydrogenase 2 (ALDH2), have been examined.[83] Thus far, no association has been reported. CYP2E1 has also been studied because it metabolises alcohol in the non-alcohol dehydrogenase pathway. Results of the CYP2E1 analyses have also been inconsistent.

Due to the male predominance in risk of HCC, investigators have examined polymorphisms in hormone-related enzymes encoded by androgen-receptor (AR), 5-alpha reductase (SRD5A2) and cytochrome p450c 17alpha (CYP17).[84] Significant associations were reported for all three loci and HCC, suggesting that variability in androgen-signalling may be associated with the risk of HCC.

Hemochromatosis and other inherited metabolic diseases

Hereditary hemochromatosis (HH) is an autosomal recessive disorder that is characterised by excessive dietary iron absorption and subsequent deposition in the parenchymal cells of the liver, pancreas, heart, joints and pituitary gland. The great majority of HH is associated with two missense mutations, C282Y and H63D, in the HFE gene on chromosome 6.[85,86]

Although the relative risk of HCC among persons with HH was originally estimated at 200, more recent studies have demonstrated the risk to be closer to 20. The risk among persons with the characteristic HFE mutations is almost certainly lower yet as it has been demonstrated that the penetrance of the mutations is not as great as it was once believed.[87] The risk is increased in the presence of a variety of cofactors including male sex, age greater than 50 years, drinking, smoking, and HBV and HCV infections.[88]

Porphyrias are the result of enzyme deficiencies in the heme biosynthesis pathway. Two types of porphyria, porphyria cutanea tarda (PCT) and acute intermittent porphyria (AIP) have been associated with increased risk of HCC.[46] The more common porphyria, PCT, has also been associated with HCV infection[89] and heterozygosity for either of the two major mutations in the hemochromatosis (HFE) gene.[90] A large prospective study of porphyrias in Sweden and Denmark, reported the risk of HCC to be higher among persons with AIP (SIR = 70.4) than among persons with PCT (SIR = 21.2), though the confidence intervals overlapped.[46]

α_1-antitrypsin (AAT) is the main proteinase inhibitor (Pi) in serum and is encoded by the AAT gene on chromosome 14.[91] A G → A substitution in exon 6, referred to as the Z mutation, results in the replacement of a glutamic acid with a lysine (Glu342Lys) and causes a conformational change in the AAT molecule. Homozygous α_1-antitrypsin deficiency is the most common genetic cause of liver disease in children.[92] PiZZ adults, particularly males, are at increased risk of both cirrhosis (OR = 7.8) and HCC (OR = 20).[93] Individuals with only one Z allele (PiZ) may also be at increased risk of liver cancer.[94] Another condition that affects children, hereditary tyrosinemia type I is an autosomal recessive condition that may lead to HCC in affected children.[95]

Obesity

In the past several years, evidence supporting an association between obesity and HCC has been growing.[96–98] Obesity is associated with conditions now believed to increase the risk of HCC, notably diabetes mellitus and non-alcoholic steatohepatitis. It has also been suggested that obesity may be responsible for a significant proportion of cryptogenic cirrhosis associated with HCC.[99] In one of the largest studies of obesity reported to date, Calle et al[97] reported significantly increased HCC risks among both obese men and women.

Diabetes mellitus

More than 20 studies of diabetes mellitus and HCC were reported between 1970 and 2004 and over three-fourths reported positive associations. Many of the studies were conducted in low-risk HCC areas such as Europe and North America, although studies from Japan also reported positive associations.

Many of the studies of diabetics also noted a relationship between diabetes and cirrhosis.[100] As insulin resistance is known to be associated with cirrhosis, it is possible that the diabetes–cirrhosis and diabetes–HCC relationships are a consequence of the fibrotic process. Cohort studies, which have found increased risks of HCC among diabetics and persons with hyperinsulinemia, suggest, however, that diabetes usually precedes the development of cirrhosis and HCC.[101] In support of these observations are studies demonstrating that hepatic steatosis is common among persons with type II diabetes.[102] Similarly, it has been suggested that the diabetes–HCC relationship is a result of HCV infection[103] due to impaired glucose and insulin metabolism.[104] Further study of the relationship will be needed as the incidence of diabetes continues to increase in most developed countries of the world.

Non-alcoholic steatohepatitis

In 1980, Ludwig et al[105] coined the term non-alcoholic steatohepatitis (NASH) to describe a condition among non-drinkers, characterised by morphologic evidence of

fatty changes in the liver with lobular hepatitis. Though subsequent definitions have varied, Brunt et al[106] proposed that NASH be defined by the presence of steatosis, inflammation, hepatocellular degenerative changes and variable fibrosis. Now recognised as the most severe form of non-alcoholic fatty liver disease (NAFLD), NASH is estimated to be the third most common liver disorder in North America[107] and the most common in Australia and New Zealand.[108]

While the majority of the patients described in the initial report of Ludwig et al[105] were female, subsequent reports have found that NASH occurs equally among males and females.[109] Conditions frequently found in association with NASH include insulin resistance, impaired glucose tolerance, type II diabetes mellitus, hypertriglyceridemia, age greater than 45 years and obesity; particularly central obesity.[108] In addition, elevated body iron stores have been reported to be common among NASH patients[110] and may be related to mutations in the HFE gene.[111] Evidence for a possible genetic component to risk has come from a study that found a high occurrence of NASH-related conditions in relatives of NASH probands.[112]

Although some early reports suggested that NASH was a non-progressive disorder, it is now recognised that severe fibrosis occurs in 15–50% of NASH patients and cirrhosis in 7–25%.[113] It has also been suggested that 'burned out' NASH is the cause of many cases of cryptogenic cirrhosis.[114] While the incidence of HCC is increased in most forms of cirrhosis[115], the risk of HCC among patients with NASH is not yet clearly defined. However, several case-reports and case-series of HCCs arising in NASH patients have been reported.[116] In addition, a case-control study in Italy[113] linked HCC to NASH-like cryptogenic cirrhosis and a record-linkage study in Denmark reported that patients with fatty liver disease were at significantly increased risk of developing liver cancer.[117] A more definitive estimate of HCC risk awaits prospective studies of NASH patients.

Natural history of HCC

Prospective studies demonstrate that HCCs begin as solitary nodules that can occur anywhere in the liver. The right lobe is more frequently involved than the left, but this may be related to its larger size. A diffuse form has been described among patients in Africa, but prospective studies have not been done to exclude the possibility that these tumours also begin as single nodules. Hepatocellular carcinomas commonly invade the portal and hepatic venous systems, producing tumour thrombi in the portal vein and its tributaries. Tumour thrombi undoubtedly occur in hepatic veins, but are more difficult to identify.[118]

The time from initial infection with hepatitis B or C viruses to the development of hepatocellular carcinoma is two to eight decades. During this long interval, many changes may occur in the liver including chronic inflammation, fibrosis, cirrhosis, increased hepatocyte death rates and regeneration. Studies of experimental hepatocarcinogenesis in animals reveal a sequence of events beginning with foci of phenotypically altered hepatocytes, proceeding to dysplastic foci and nodules.[119] The continuous cycle of cell death and regeneration may eventually result in the proliferation of hepatic stem cells morphologically recognisable as oval cells[120,121], although mature hepatocytes are the major source of cell replacement in the damaged liver.[122] Oval cells may give rise to the phenotypically altered foci, but whether the oval cell is the precursor cell of HCC is unclear.

Primary prevention

Chronic HBV infection, which is the cause of the largest proportion of HCCs in the world, is 90% preventable with proper use of the hepatitis B vaccine.[123] Studies from Taiwan, where universal immunisation of newborns was introduced in 1984, have shown a 50% reduction in the incidence of HCC among adolescents.[14] As the vaccinated population moves into their late teens and early 20s, it will be important to see whether the magnitude of protection is maintained. The challenge now is to expand hepatitis B vaccination coverage to the populations at greatest risk of HBV infection and HCC. Universal vaccination of newborns has been adopted by almost all developed countries and vaccination programs are being introduced into the 72 poorest countries of the world.[123] Vaccination programs will reduce the prevalence of chronic HBV infection in endemic areas from between 8% and 20% to less than 2%[124] and this should lead to major decreases in the incidence of HCC in coming decades.

Currently, there is no vaccine for the prevention of HCV infection. Nevertheless, the incidence of HCV infection has been declining in the United States and other developing countries because of screening of blood and organ donors and reduction of transmission among injecting drug users (IDUs). Annual new HCV infections have decreased from about 230 000 in the 1980s to 30 000 in 2000.[12] Further reduction in the transmission of HCV can be achieved by counselling IDUs about risks of sharing drugs, syringes and needles; providing disposable needles; and enrolling IDUs in substance abuse treatment programs.[12]

Whether HCC incidence would be affected by reducing exposure to AFB_1 is uncertain. In China, the government has replaced corn, the main source of AFB_1, with rice as the primary staple food in high HCC incidence areas. HCC incidence has declined modestly. Limiting fungal contamination of crops either pre- or post-harvest to reduce AFB_1 exposure could involve low technology post-harvest measures or genetically engineered crops resistant to fungal infection or toxin biosynthesis.[125]

Reduction of alcohol consumption by HCV infected individuals could have a profound effect on HCC risk. Although treatment of alcohol abuse is notoriously difficult, physician's advice and self-help booklets can cause problem drinkers to reduce their consumption by 25%.[126] Therefore, a public health strategy of reducing alcohol intake to one to two drinks a day rather than abstention might significantly impact the risk of cirrhosis and HCC.

Chemoprevention

Several chemopreventive agents have been examined in HCC, though not many have moved beyond animal studies. The aim of chemoprevention has been to prevent cirrhosis because prevention of HCC in non-HCV-related cirrhosis has been unachievable. Among HCV-infected individuals, the efficacy of α-interferon in reducing HCC risk has been demonstrated, even among patients who did not achieve a sustained response.[18,127] Unfortunately, α-interferon appears to have little effect in diminishing HBV associated HCC risk.[128,129] Whether therapy with nucleoside inhibitors like Lamivudine and Adefovir dipivoxil will reduce the risk of HCC among HBV-infected patients is unknown, but the improvement in liver histopathology with prolonged treatment with these drugs is encouraging.[130] Several other chemopreventive agents are at pre-clinical or early phase clinical stages of development .

Practice points

- more than 80% of all hepatocellular carcinomas are caused by chronic infection with either hepatitis B virus (HBV) or hepatitis C virus (HCV)
- HBV infection is preventable with a safe effective vaccine; HCV infections are largely preventable by public health measures
- prevention of infection with these viruses would prevent most cases of HCC
- treatment of established HBV and HCV infections reduces, but does not eliminate, the risk of developing HCC

Research agenda

- the causes of increasing rates from HCC in the United States and other countries need to be identified
- the factors that are responsible for the great variation in outcomes of chronic HBV and HCV infections need to be defined
- whether the metabolic syndrome is a cause of HCC needs to be established, and if it is a cause, the factors involved in causation need to be identified
- simple methods to reduce exposure to aflatoxin, a major co-factor of HCC in Africa, need to be developed

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